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# Value of diazepam ('Valium') in treatment of cardiac arrhythmias

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*Diazepam did not alter the rate or rhythm in 111 patients with atrial fibrillation. In 3 out of 38 patients with atrial flutter the use of diazepam was followed by an increase in atrioventricular block. Diazepam restored sinus rhythm in 1 patient with atrial tachycardia (total 7 patients) and in 1 patient with ventricular tachycardia (total 8 patients). Experimentally in the dog diazepam raised the electrically-induced ventricular tachycardia threshold significantly. Pretreatment with diazepam did not alter significantly the dose of strophanthidin K required to induce ventricular tachycardia in the dog.*

*The value of diazepam as a cardiac anti-arrhythmic agent should be further assessed in a controlled clinical trial, especially in patients with acute myocardial infarction.*

It has recently been suggested that diazepam ('Valium') has cardiac anti-arrhythmic properties (Van Loon, 1968; Papp, 1969). This drug has been used alone for heavy sedation before electrical conversion of arrhythmias in our department for the past 2 years. We have studied the anti-arrhythmic properties of diazepam in the clinical setting and in experimentally-induced arrhythmias in the dog. The purpose of this paper is to report our findings.

## Clinical study

**Material and methods** Diazepam was given intravenously (5–75 mg.) to 142 patients on 164 different occasions before attempting electrical conversion of an arrhythmia. These arrhythmias were atrial fibrillation (111 instances), atrial flutter (38), supraventricular tachycardia (7), and ventricular tachycardia (8). Diazepam was given to these patients for its sedative and hypnotic effect, and its use allowed direct current (DC) shock therapy to be given without general anaesthesia and tracheal intubation.

## Results

The major underlying pathology in our patients was rheumatic heart disease (112 cases), ischaemic heart disease (19 cases), undetermined or 'lone' (5 cases), chronic lung disease (4 cases), and treated thyrotoxicosis (3 cases). The remaining 17 patients suffered from combinations of these diseases and miscellaneous other conditions. In none of the 111 episodes of atrial fibrillation was the rhythm influenced by the administration of diazepam. Of 38 patients with atrial flutter, there were 3 instances of increased atrioventricular block following diazepam. One patient with supraventricular tachycardia (total 7 cases), and one with ventricular tachycardia (total 8 cases) reverted to sinus rhythm immediately after receiving diazepam.

Illustrative cases are briefly reported.

**Case 1: atrial flutter** A 73-year-old woman was admitted to hospital in April 1969, with a diagnosis of ischaemic heart disease and left ventricular failure. Examination revealed gross cardiomegaly and congestive cardiac failure. An electrocardiogram showed atrial flutter with 2:1 block and a ventricular rate of 135. Cardioversion was contemplated and the patient was given 5 mg. diazepam intravenously. After this the rhythm changed to atrial flutter with 4:1 block. The patient was therefore not cardioverted but was digitalized. The patient reverted to sinus rhythm three days later.

**Case 2: atrial tachycardia** A 58-year-old man developed atrial fibrillation after his second myocardial infarct in March 1967. The patient was admitted to hospital in February 1969, and after a test dose (200 mg.), was given quinidine (400 mg.) every 2 hours for 3 doses (total 1400 mg.). With this, atrial tachycardia occurred. This rhythm was unaltered by carotid sinus pressure. The patient was given diazepam (5 mg.) intravenously with the intention of electrically con-

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verting his rhythm. Immediately after this injection sinus rhythm was noted.

**Case 3: ventricular tachycardia** A 65-year-old man had a long history of peripheral vascular disease. He was admitted to hospital in March 1969, with a 6-day story of a painful, cold left leg. An electrocardiogram showed sinus rhythm and a possible old inferior infarct. The patient responded well to bed-rest and intravenous heparin therapy. The heparin was reduced 10 days after admission and discontinued a day later. On that morning the patient complained of the sudden onset of severe, constricting chest pain. This was accompanied by breathlessness and sweating. An electrocardiogram showed ventricular tachycardia (rate 190 a minute). Lignocaine (100 mg.) was given intravenously without effect and the patient was given diazepam (5 mg.) intravenously before cardioversion. Immediately after the injection he reverted to sinus rhythm. Serial electrocardiograms and enzyme studies did not show a further myocardial infarction.

## Experimental studies

**Material and methods** The effect of diazepam on the 'ventricular tachycardia threshold' as described by Lown and associates (Lown, Kleiger, and Williams, 1965) was studied. For this study 12 mongrel dogs of both sexes were used. The dogs weighed between 11·8 and 23·2 kg. (average 18·0 kg.). Anaesthesia was induced with sodium pentobarbitone given intravenously (30 mg./kg.). Respiration was maintained with a Harvard pump using room air and a cuffed endotracheal tube. The minute volume was adjusted to maintain the arterial oxygen saturation in excess of 95 per cent. At regular intervals 'sighing' was induced manually. Catheters were inserted into the femoral artery and vein. Arterial blood pressure was monitored continuously using a Statham P23 Db strain gauge.

Direct current shocks were given externally using a Corbin-Farnsworth defibrillator. The electrode paddles measuring 9 cm. in diameter were covered with conductive paste and applied with pressure on either side of the shaved chest at the level of the cardiac apex beat. The sites were marked and used on each occasion.

The DC shock was synchronized with the electrocardiogram to occur 18 milliseconds after the peak of the R wave. To determine the ventricular tachycardia threshold, shocks were given every 10 seconds. The ventricular tachycardia threshold was defined as the energy level at which 3 consecutive DC condensor discharges produced a run of 3 or more consecutive ventricular complexes, with abnormal QRS configuration at a rate exceeding 60 a minute, and occurring within 3 seconds of the shock. The initial shock was given at an energy setting of 40 or 60 watt seconds (w.sec.). If ventricular tachycardia developed (positive response), the energy was reduced to 20, and then 10 w.sec. If it did not occur (negative response), the energy level was increased progressively to 80, 100, 200, 300, and 400 w-sec.

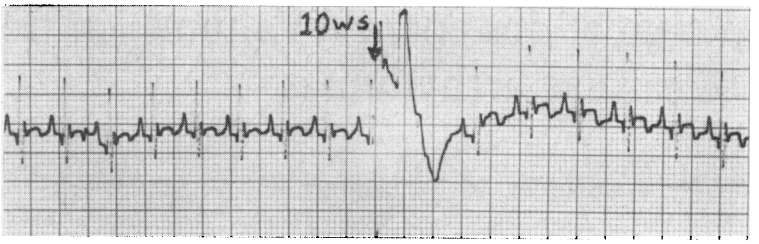


FIG. 1 *Negative response, no ventricular dysrhythmia occurring after a 10-watt second shock.*

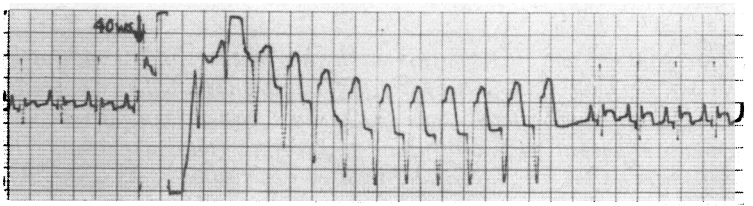


FIG. 2 *Positive response. Ventricular tachycardia produced by a 40-watt second shock.*

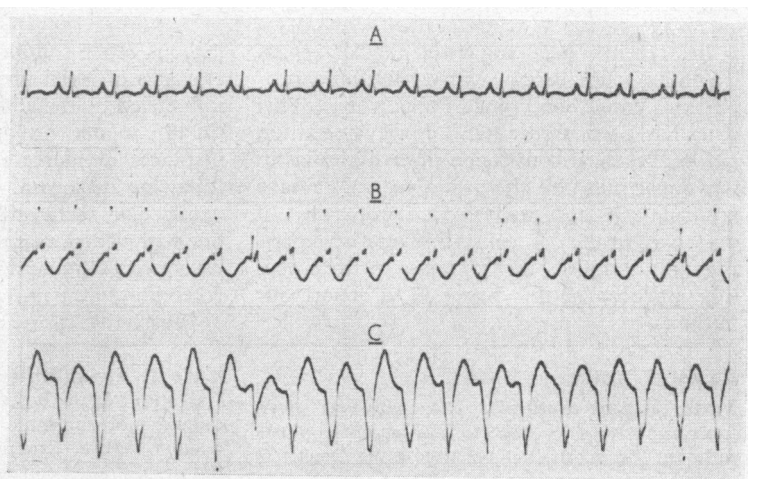


FIG. 3 *Digitalis intoxication. (A) control tracing; (B) supraventricular tachycardia with aberration; and (C) ventricular tachycardia.*

Fig. 1 and 2 illustrate negative and positive responses respectively.

In 8 dogs a stable control period of 60 to 95 minutes was established before giving diazepam. The threshold during this period was determined every 15 minutes. Diazepam was given rapidly intravenously as a single dose of 20 mg. Thresholds were then measured after 5 minutes, after a further 10 minutes, and subsequently every 15 minutes for a total of 90 minutes after giving the drug. In 4 dogs, thresholds were determined at 15-minute intervals for 4 hours without giving diazepam.

In a further experiment, each of 5 different dogs weighing 13·6 to 21·8 kg. (average 17·3 kg.) were studied twice at weekly intervals. The dose of strophanthidin K ('Strophosid') necessary to produce toxicity (stable ventricular tachycardia) was determined by infusing the drug at a rate of 100 μg. a minute for 5 minutes, followed by 50 μg. every 5 minutes until supraventricular tachycardia or ventricular ectopic beats occurred. Then 50 μg. was given every 10 minutes until ventricular tachycardia occurred (Fig. 3). In one of the two studies which were performed in random order, the dog was pretreated with diazepam (20 mg.) 15 minutes after induction of anaesthesia. After a further 15 minutes, strophanthidin K was infused until toxicity occurred. In both experiments the strophanthidin dose schedules were identical.

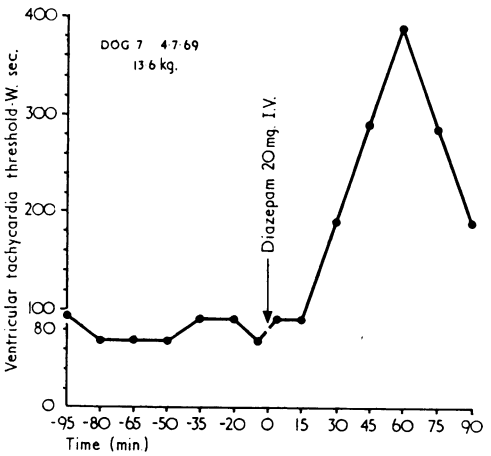


FIG. 4 *'Ventricular tachycardia threshold' before and after giving diazepam.*

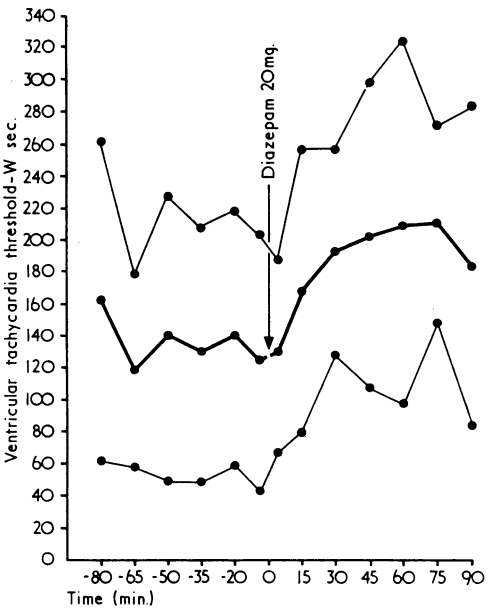


FIG. 5 *'Ventricular tachycardia threshold' in 8 dogs before and after giving diazepam. The mean values (± 1 SD) are shown.*

## Results

Eight dogs were studied to determine the ventricular tachycardia threshold before and after giving diazepam. These dogs maintained a satisfactory acid base balance throughout the experiment and had control thresholds between 40 and 300 w.sec. In one, the threshold did not change after giving diazepam. The remaining 7 dogs showed a rise in threshold after diazepam. The mean threshold before diazepam was 142 w.sec. (SD 87·1). After diazepam the mean threshold rose to 187 w.sec. (SD 86·2). The difference in these values is significant at the 5 per cent level ($t = 2·577$). In Fig. 4 a typical rise of ventricular tachycardia threshold after the administration of diazepam is illustrated. In Fig. 5 the mean values for all dogs are depicted. Four dogs that were not given diazepam had thresholds determined every 15 minutes over a 4-hour period. No significant change in threshold was observed during this period.

Five further dogs were each studied twice to determine the dose of strophanthidin K required to produce ventricular tachycardia with and without pretreatment with diazepam. The mean dose of the glycoside without diazepam was 1200 μg. (SD 127·5), while that after giving diazepam was 1180 μg. (SD 266·0). This difference is not statistically significant. The mean time from the beginning of the strophanthidin infusion to the development of ventricular tachycardia was 72·4 minutes (SD 25·3) in the absence of diazepam, and 64·0 minutes (SD 44·3) after pretreatment with diazepam. The difference in these values is also not statistically significant.

## Discussion

Diazepam, a synthetic benzodiazepine derivative has been used for the control of anxiety states (Randall *et al.*, 1961), in tetanus (Hendrickse and Sherman, 1965), and in the treatment of epilepsy and spastic neuromuscular disorders (Gastaut *et al.*, 1965; Lombroso, 1966; Gordon, 1966; Calderon-Gonzalez and Mireles-Gonzalez, 1968). It has also been used as premedication for anaesthesia (Brandt and Oakes, 1965), for the induction of anaesthesia (McClish, 1966), and to induce narcosis before direct current cardioversion (Nutter and Massumi, 1965; Kernohan, 1966). McClish (1966) demonstrated transitory minimal

degrees of hypotension, bradycardia, and respiratory depression after the use of this drug. Lown (1964) reported that diazepam had no significant effect on respiratory, circulatory, or autonomic nervous systems.

In epilepsy, associated with post-traumatic scars and expanding lesions, the epileptogenic region of tissue forms a boundary between the lesion and the histologically normal cortex. The ectopic ventricular impulses that occur within a few minutes after abrupt occlusion of a coronary artery, arise in partly ischaemic tissues which form a margin round a potential infarct (Harris, 1948). The apparent similarities between the origin of ectopic ventricular activity after coronary occlusion and that of focal epileptic discharges suggest that drugs that prevent epilepsy might also suppress ventricular arrhythmias, especially those accompanying acute myocardial infarction. This thesis was first tested by Harris and Kokernot (1950), using diphenylhydantoin. More recently, others have confirmed the value of this drug in controlling cardiac arrhythmias, especially those induced by digitalis (Conn, 1965; Ruthen, 1965). In theory, therefore, diazepam, a potent anti-epileptic agent, might be expected to have cardiac anti-arrhythmic properties.

In a case report, Van Loon (1968) described an 88-year-old man who suffered an anterior myocardial infarct and had persistent ventricular arrhythmias. These arrhythmias could not be controlled with lignocaine, diphenylhydantoin, antazoline, or procainamide, but both the multiform ventricular ectopic beats and ventricular fibrillation were replaced by normal sinus rhythm within 4 minutes of giving 10 to 20 mg. diazepam intravenously. Diazepam was given on 3 separate occasions and was followed by sinus rhythm which lasted between 15 and 90 minutes.

Muenster and co-workers (1967) compared the use of sodium thiopental with diazepam anaesthesia (15 to 20 mg. given intravenously over 60 to 90 seconds) for direct current shock therapy in two similar but small groups of patients with atrial fibrillation. After giving sodium thiopental, but before the shock, premature ventricular systoles occurred frequently. No premature ventricular systoles were observed in the group that received diazepam. After the shock, frequent premature ventricular systoles persisted in the group given sodium thiopental, whereas the patients who received diazepam had significantly fewer premature ventricular systoles. These findings may be interpreted as indicating that diazepam has an anti-arrhythmic effect. An alternative explanation, however, is that diazepam has no anti-arrhythmic effect, but that sodium pentothal induces ventricular ectopic beats.

Winters and associates (1968), using diazepam intravenously in doses of 10 to 40 mg. for 21 elective direct current countershock procedures for ventricular and supraventricular arrhythmias in 18 patients, found no significant changes in heart rate, blood pressure, or respiratory rate. One episode of ventricular arrest occurred, however, in a 56-year-old negro woman with atrial tachycardia complicating an atrial septal defect. The authors did not relate this episode to the use of diazepam. It seems at least likely, however, that diazepam was responsible for this cardiac arrest, and, of course, most anti-arrhythmic agents are capable of producing cardiac arrest.

Papp (1969) stated that diazepam (10 to 20 mg. intravenously) 'has also been effective in ventricular arrhythmias'. No evidence is cited, however, for this conviction. Despite the widespread use of diazepam in clinical practice, no other reports concerning its cardiac anti-arrhythmic properties have appeared.

Our clinical experience has been that diazepam has no effect on established atrial fibrillation. Unfortunately we have no details on the incidence of ectopic beats in our patients with atrial fibrillation before and after cardioversion. Diazepam can, therefore, not be compared with other anaesthetic agents in this respect. Our finding that increased atrioventricular block occurred after giving diazepam in 3 out of 38 patients with atrial flutter suggests that diazepam is not quinidine-like in action. Quinidine in the undigitalized patient has long been known to reduce the atrial rate in atrial flutter without significantly reducing atrioventricular conduction, thereby often paradoxically increasing the ventricular rate. A similar effect has also been described after the use of lignocaine, antazoline, and diphenylhydantoin (Dreifus, Rabbino, and Watanabe, 1964; Grissom *et al.*, 1967; Adamson and Spracklen, 1968).

A decrease in atrioventricular conduction would be expected with a propranolol-like drug. Diazepam, however, did abolish atrial tachycardia in one of our cases. This effect, together with slowing of atrioventricular conduction in atrial flutter, is found with parasympathomimetic agents, like edrophonium chloride (Tensilon) (Moss and Aledort, 1966). While coincidence cannot be excluded, our clinical findings suggest that diazepam might have cardiac anti-arrhythmic properties. Certainly controlled trials with diazepam are warranted, especially with regard to the inci-

dence of arrhythmias after myocardial infarction.

For our experiments with diazepam we chose two well-established models, namely electrically-induced and digitalis-induced ventricular arrhythmias in the dog. We have closely followed the technique of Lown and associates (1965) for inducing ventricular tachycardia with a commercially available external defibrillator. Like Lown we found that this technique gave stable 'thresholds' over prolonged periods. Attention was paid to smooth, maintained anaesthesia, adequate ventilation, and the avoidance of hypothermia. With these provisos the preparation was found to be stable in our hands for at least 4 hours. Lown has reported stability of threshold for a period of 7 hours. A rise in electrically-induced ventricular tachycardia threshold was found in 7 out of 8 dogs receiving diazepam. The control thresholds were lower in younger and smaller dogs. We found a rise, however, after diazepam whether the control value was high or low. A wide range of thresholds (40 to 300 w.sec.) is reflected in the large standard deviation of the mean values (Fig. 5).

While we have shown that diazepam raised the ventricular tachycardia threshold significantly ($p < 0.05$), the interpretation of this finding is difficult. Lown and associates (1965) have shown that digitalis dramatically lowers the ventricular tachycardia threshold. Wittenberg and Lown (1969) showed that dextropropranolol (a drug with a non-specific anti-arrhythmic action, but with virtually no beta adrenergic blocking effect) and propranolol restored the ventricular tachycardia threshold to normal after it had been reduced with ouabain. ICI 50,172, a pure beta-blocking agent, did not have this effect. The effect of other anti-arrhythmic agents on this threshold has not been reported. It would be prudent at this stage, therefore, not to assume that an agent which raises the ventricular tachycardia threshold is necessarily anti-arrhythmic in the clinical setting. Bacaner (1966, 1968a), however, has shown that the vulnerability of the dog heart to ventricular fibrillation provoked by directly-applied electric shocks is reduced by treatment with bretylium tosylate. The same author has also found this agent to be effective clinically in the treatment of ventricular fibrillation and other ventricular arrhythmias (Bacaner, 1968b).

Our finding that diazepam is ineffective in the prophylaxis of digitalis-induced ventricular tachycardia in anaesthetized dogs should not exclude this agent from further trials in the management of digitalis-induced arrhythmias. Diphenylhydantoin and beta-adrenergic blocking agents are of proven value in the treatment of digitalis-induced arrhythmias in man (Conn, 1965; Ruthen, 1965; Lang *et al.*, 1965). Experimentally, however, there is conflicting evidence whether pretreatment with diphenylhydantoin and beta-adrenergic blocking agents protect against digitalis-induced arrhythmias (Vaughan Williams and Sekiya, 1963; Lucchesi, 1964; Aroesty and Cohen, 1966; Scherlag *et al.*, 1968; Zeft *et al.*, 1969). Nevertheless both diphenylhydantoin and beta-adrenergic blocking agents signicantly shorten the duration of digitalis-induced ventricular tachycardia when given shortly after the onset of the arrhythmia (Zeft *et al.*, 1969). Further work is therefore needed to determine if diazepam is of value in the therapy of digitalis-induced arrhythmias in man.

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